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INTRODUCTION TO SIX SHORT PAPERS ON THE PRESENT STATUS OF CLINICAL HEMODIALYSIS

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BOTH gradual improvements and sudden innovations have enhanced the usefulness of the artificial kidney in the treatment of uremia; this is true both for acute and for chronic renal failure.

Patients who are very sick, very young, or very old, can now be treated with dialysis and ultrafiltration.

The danger of hemorrhage is no longer a contraindication, since it is possible to heparinize the blood in the machine without prolonging the clotting time of the patient's blood.

Growing experience in the treatment of barbiturate poisoning makes dialysis preferable over conservative management in all really serious cases.

The application of very frequent, daily, or even continuous dialysis makes it possible to reduce levels of urea, creatinine, uric acid, and other retention products to normal or nearly normal levels. This technic relieves the symptoms of uremia such as nausea, vomiting, and twitching, and helps to avoid many of the complications that were formerly expected in patients in renal failure. Most important, this intensive dialysis seems to reduce the chance of infection, particularly of bronchopneumonia.

Large amounts of water can be removed by the artificial kidneys by ultrafiltration. Among the most dramatic clinical results of dialysis are the effects of ultrafiltration upon the dyspnea and cyanosis of patients with pulmonary edema. In our experience a 90-minute dialysis plus ultrafiltration has never failed to improve the clinical symptoms of pulmonary edema, although the patchy design

may still be evident on roentgenograms of the chest. A patient with intractable cardiac edema can be treated with dialysis and ultrafiltration and, after an initial improvement, may respond to diuretics to which he had previously been refractory. Ascitic fluid has been desalted and concentrated by ultrafiltration and dialysis in the artificial kidney. After intravenous administration of the concentrate, a so-called stabilization of ascitic formation was observed so that no further paracenteses were required.

The artificial kidney has been combined with artificial hibernation or refrigeration in patients who were not only uremic, but also hyperpyrexic, and in patients who were failing so rapidly that refrigeration seemed to be the only possibility of halting a progressively disastrous course.

The simultaneous treatment of two patients on one commercially available twin-coil kidney has greatly reduced the cost and number of personnel needed for operation of the machine.

Finally, technical advances are coming into sight for the making of new artificial kidneys. Heat-sealable dialyzing membranes will revolutionize the design of present dialyzers. Exchange resins may even make them obsolete.

Until recently, the artificial kidney was used mainly for patients in acute renal failure. The work of Dr. Belding H. Scribner and his associates[1] has opened the field for the treatment of patients in chronic renal failure. Periodic reductions of retention products, and normalization of serum electrolyte and water balance in these patients are possible by continuous dialysis for 24 hours once every five days. This entirely new approach not only prolongs life and makes it comfortable, but, it is hoped, will keep the patients in a condition good enough to be usefully employed.

This review comes at an opportune time since a generous grant from The Hartford Foundation enables the artificial kidney team at the Cleveland Clinic to explore further the potentials of intermittent dialysis for patients in chronic renal failure.

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THE USE OF THE ARTIFICIAL KIDNEY IN ACUTE INTOXICATION BY HYPNOTIC DRUGS

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IN the last few years the artificial kidney has been used successfully in the treatment of acute poisoning by the hypnotic drugs, glutethimide (Doriden†), barbiturates, and bromides.[1,2] In 1958, Schreiner[1] outlined the basic conditions in acute poisoning which are necessary for effective hemodialysis. The poison molecule must be readily diffusible from plasma water and well distributed within accessible body-fluid compartments. The toxicity of the molecule must be proportional to the concentration of the drug in the serum and to the duration of bodily exposure. Furthermore, the amount of poison removable by dialysis must be a significant addition to the amount that can be successfully removed by the slower physiologic mechanisms.

In practice, we adhere to the principle that the patient who has taken an overdose of hypnotics should be given conservative treatment if the coma is light and if he is observed closely for a gradual improvement as judged from the vital signs and the neurologic examination. However, hemodialysis is justified in any one of three conditions:[2] (1) when the amount of poison ingested or the initial concentration of poison in the blood is unquestionably known to be in the fatal range, (2) when the patient's condition is deteriorating, and (3) when prolonged coma would be harmful as in the debilitated or elderly patient. Therefore, the acceleration, by dialysis, of recovery from coma is justifiable since a reduction in morbidity in turn reduces the mortality rate.

Eight patients with hypnotic drug intoxication have been dialyzed at Cleveland Clinic Hospital since 1957. The intoxications had been caused by the ingestion of glutethimide (one patient), secobarbital sodium (one patient), phenobarbital (one patient), barbiturates of unknown type (three patients), and a combination of barbiturate and glutethimide (two patients). Eleven dialyses were performed in the eight patients and excellent results were obtained in seven patients. One patient was dialyzed two times and one patient three times.[2] The latter patient, who died, had ingested barbiturates, glutethimide, reserpine, and oxanamide. She was treated with two consecutive dialyses upon admission; the third dialysis was administered because of persistent coma five days following the first dialysis. Approximately 10 hours after the last dialysis the patient died of bilateral bronchopneumonia. Schreiner[1] reported a case of acute barbiturate poisoning in which three dialyses were performed. Several hours after the first dialysis, which had caused

This study was prepared under the guidance and sponsorship of W. J. Kolff, M.D., Head of the Department of Artificial Organs.

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†*Doriden (glutethimide N.N.D. CIBA), CIBA Pharmaceutical Products Inc.*

dramatic improvement, the concentration of barbiturates in the patient's blood was greater than the initial concentration, and the clinical condition was worse than initially. This course was attributed to recovery of an atonic bowel and consequent absorption of residual barbiturate. The patient underwent two more dialyses on the first and third days following the initial dialysis, after which there was an uneventful recovery. In retrospect it is believed by Nakamoto and Kolff[2] that the patient, who died, should have been given three dialyses in rapid succession, to decrease the level of coma quickly and thus perhaps avoid the complication of pneumonia.

Hemodialysis should be the most effective method to relieve bromide intoxication. The artificial kidney removes bromide rapidly from the circulating blood, and replaces it with chloride, unlike the natural kidney, which does not distinguish between bromide and chloride.[3,4] Relief of bromide intoxication usually is achieved by conservative measures in from one to several weeks. However, in Schreiner's[1] patient, relief of a semicomatose, psychotic state was accomplished in 18 hours after a six-hour dialysis in which the concentration of sodium bromide in the blood decreased from more than 350 mg. per 100 ml. to approximately 40 mg. per 100 ml.

Conclusion

In treating acute intoxication from hypnotic drugs, we do not underestimate the value of the conservative approach with regard to the maintenance of an adequate airway, electrolyte and fluid balance, and support of the blood pressure and respiration. However, when the proper conditions for hemodialysis are present, we believe that, rather than use of the conservative approach alone, one treatment or several consecutive treatments with the artificial kidney offer the patient a better chance of survival.

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USE OF RENAL BIOPSY TO PREDICT THE CLINICAL RESULT OF HEMODIALYSIS IN CHRONIC RENAL DISEASE

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IN spite of the growing use of hemodialysis and the increasing appreciation of the value of the renal biopsy, we have been unable to find reported series that correlate the two procedures. It has been noted in general, however, that the "worse the glomerulus, the worse the prognosis".[1] When patients in chronic renal failure did not respond to the best medical management we were able to give them, they were considered to be candidates for dialysis. Therefore, we have been able to observe the course of many patients with chronic uremia who received treatment with the artificial kidney. Renal biopsy studies were done in some of those patients and the results are discussed in this report.

Materials and Methods

Seventeen patients who had chronic renal failure for more than one month, and who each required at least one hemodialysis, each had a diagnostic needle biopsy of the kidney soon after initial admission to the hospital.† Their ages ranged from 14 to 64 years, with an average of 41 years. Each dialysis was performed with a twin-coil disposable artificial kidney.[2]

Each renal biopsy specimen was analyzed according to its individual components. The histopathologic changes of the glomeruli were graded from 0 to 3+ as observed with light microscopy: 0, essentially normal glomeruli; 1+, damage involving at least one of the glomeruli (cellular proliferation, capsular adhesions, or thickening of the basement membrane); 2+, destructive changes involving from one-third to two-thirds of the glomeruli; 3+, destruction of the glomerular pattern of more than two-thirds of the glomeruli *(Fig. 1)*. Other histopathologic changes studied included evidence of tubular alterations, variations in the interstitium, and vascular damage.

The histopathologic changes of each renal specimen were correlated with the patient's history, the physical examination (such as the duration of symptoms prior to admission, degree of edema, funduscopic changes, blood pressure); serum albumin content, the initial blood studies, urinalysis, urinary urea and electrolytes, renal size (determined from roentgenograms), daily urinary volumes, and the clinical course while in the hospital.

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†Many of the patients were under the joint care of Dr. David C. Humphrey, the Department of Hypertension and Renal Disease, and Dr. Willem J. Kolff, the Department of Artificial Organs. Most of the renal biopsies were performed by Dr. Eugene F. Poutasse, the Department of Urology.

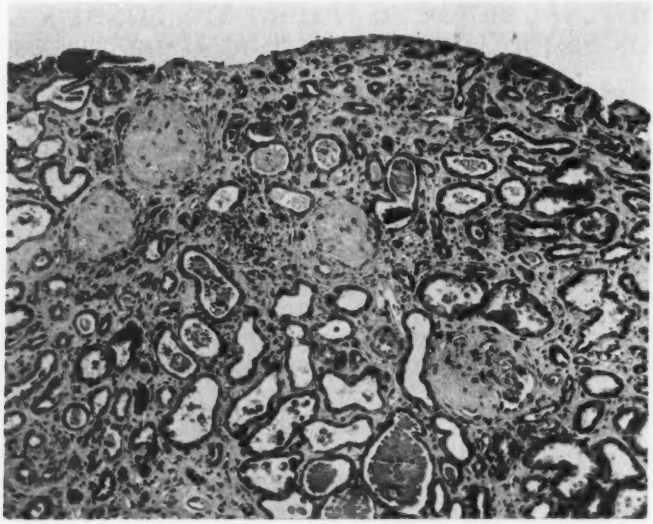

Fig. 1. Photomicrograph of a needle biopsy specimen showing chronic sclerosing and proliferative glomerulonephritis of severe degree, hematoxylin and eosin stain; magnification X 120.

The clinical responses to hemodialysis were graded from 0 to 3+, determined at the time of death, or at time of discharge after the first hospital admission. Death is designated by 0; 1+, uremia that was progressively worse after each dialysis with no hope of arresting the disease; 2+, stability of the uremic state at the time of discharge; 3+, azotemia approaching normal levels. The 2+ and 3+ responses to treatment are considered favorable; the 0 and 1+ responses, unfavorable.

Results and Correlations

The most important and significant correlation is illustrated in *Figure 2*—the severity of the glomerular changes and the therapeutic response in chronic glomerulonephritis. Of the five patients with favorable responses (2+ or 3+) to hemodialysis, only one patient had more than 60 per cent glomerular destruction. On the other hand, of the 11 patients with severe glomerular destruction (3+) only one patient had a favorable response to hemodialysis. There was little correlation between the degree of vascular histopathologic changes and the clinical response to dialysis. The degree of tubular changes, especially atrophy, seemed to parallel the range of glomerular change.

The presence of aggravating or associated illness such as essential hypertension, congestive heart failure, or infection did not affect the final outcome to any noticeable extent. The prognosis was unrelated to the age of the patient. Although the results in patients with fundal hemorrhages, exudates, or papilledema were

less favorable than those in patients free of these conditions, the changes were unrelated to histopathologic changes. Of particular importance is a lack of correlation of renal size, as determined by the roentgen examination, and the prognosis or the response to therapy.

Of the three patients who had stabilized azotemia (2+) at the time of discharge, one died six months and one three months later; however, after dialysis they

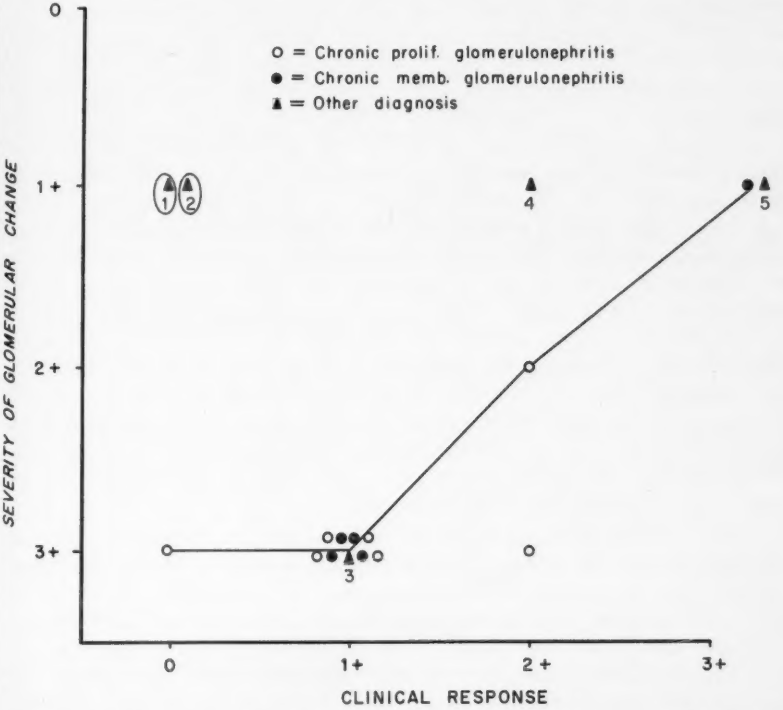

Fig. 2. Graph showing the correlation of the clinical responses of patients treated with the artificial kidney with the extent of glomerular damage as determined by the histopathologic changes in specimens from needle biopsies of the kidneys. For the ordinate, 0 means no pathologic changes and 3+ means more than two thirds of the glomeruli destroyed. For the abscissa, 0 means death of the patient and 3+ means improvement of the patient's condition with loss of azotemia. The triangular markers denote renal disease other than chronic glomerulonephritis. The two encircled markers are excluded from the final evaluation of results, as they are dependent upon factors other than primary renal disease. Patient 1 had primary hyperparathyroidism with nephrocalcinosis and pyelonephritis, and died of a cerebral accident. Patient 2 had severe primary malignant hypertension. Patient 3 had subacute glomerulonephritis with its typically fatal course within a few months. Patient 4 had "pure" chronic pyelonephritis, but only one glomerulus was seen in the biopsy specimen. Patient 5 had membranous glomerulonephritis.

enjoyed life with moderate strength and comfort. The third patient, who is alive seven months later, is becoming cachectic and must undergo repeated hemodialyses.

Discussion

When should the clinician employ the artificial kidney to treat uremia in chronic renal disease? It is a foregone conclusion that hemodialysis will be of immediate benefit; but the ultimate prognosis or even the response during the immediately postdialytic hospital course has not been predictable. Death is usually the final outcome as measured in months after diagnosis, but we believe that the survival interval often may be lengthened and that the patient may be offered a more comfortable existence by using dialysis rather than conservative treatment alone.

Our results suggest that the renal biopsy study is the best method of selecting those patients who may benefit from hemodialysis. Those with little or no glomerular destruction responded favorably to this vigorous treatment, whereas only 1 of 11 patients with severe glomerular destruction responded favorably for longer than a few days. The urinary output and fundal changes are helpful but not dependable factors in regard to prognosis. The presence or absence of hypertension or the size of the kidneys seems to be of no prognostic help.

The general diagnosis, usually best established by renal biopsy, also may be of importance in predicting the prognosis. Most of the 17 patients in our series were diagnosed as having some form of glomerular disease. It seems that patients with polycystic disease or chronic pyelonephritis with no overwhelming glomerular destruction have a more protracted course of renal failure and are more likely to be benefited by dialysis,[3-5] even in the end stage of the disease, than are patients having primary glomerular disease.

There is a need for much additional study to correlate the course of chronic renal disease with the histopathologic evidence from renal biopsy specimens. According to our analysis, renal biopsy seems to be of definite value to the clinician in selecting patients who might benefit for more than a few days after treatment with the artificial kidney. However, in the near future, improvements in the artificial kidney may overcome its limitations of today. Since it has been possible to maintain patients without excretory function for 74 days,[6] and more than 80 days,[7] and for five months,[8] dialysis is limited only by practical impediments and not by theoretic principles.

Summary

Seventeen patients with severe chronic renal disease required treatment with the disposable artificial kidneys. Their clinical responses during the first hospital admission were correlated with the histopathologic evidence in renal biopsy specimens and with the important clinical and laboratory studies. The extent of glomerular destruction seems to be the best means of predicting the response to treatment with the artificial kidney. The need for more extensive studies is stressed.

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REMOVAL OF EDEMA FLUID BY ULTRAFILTRATION WITH THE DISPOSABLE TWIN-COIL ARTIFICIAL KIDNEY

Report of Two Cases

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THE artificial kidney is useful not only for the treatment of the uremic state but also in the removal of edema. The states of overhydration[1-3] in which hemodialysis can be effective are those in which the kidneys either cannot excrete water, as in advanced renal failure, or will not excrete water, as in intractable cardiac failure. The frequency of overhydration in azotemia is emphasized by the fact that of the last 100 patients who underwent dialysis at the Cleveland Clinic Hospital, 35 required ultrafiltration to remove excess fluid.

During hemodialysis, fluid can be removed either by raising the pressure in the dialyzing unit, which results in ultrafiltration, or by raising the solute concentration of the rinsing fluid which, by osmosis, causes a movement of water from the less concentrated plasma inside the cellophane tubing of the artificial kidney to the more concentrated fluid of the bath. To effect ultrafiltration, the pressure in the disposable twin-coil artificial kidney[4] can be increased by constricting the outflow tract with a screw clamp. The pressure in the outflow tract of the artificial kidney, proximal to the clamp, is measured by a Tycos manometer connected to the bubble-catcher system, as shown in *Figure 1.* The pressure in the bubble catchers can be safely increased to 300 mm. of Hg without rupturing the cellophane tube. The pressure at the point where the blood leaves the coil is approximately 40 mm. of Hg above that in the bubble catchers, with about 50 cm. of difference in height from the twin-coil artificial kidney to the bubble catchers. Fluid removal by ultrafiltration with a twin-coil artificial kidney can be easily measured when a known volume of blood is circulated through an artificial kidney from a calibrated reservoir *(Fig. 2).* The rate of fluid removal can be increased approximately from 100 to 600 ml. per hour by increase of ultrafiltration, and further to 1200 ml. per hour by combination with osmosis, if dextrose is added up to 10 per cent in the rinsing solution. There is also, generally, an increase in the amount of fluid removal with an increase in blood flow rate through the artificial kidney.

During hemodialysis the rate of fluid exchange between the patient and the rinsing solution is an important factor in the clinical management of the patient's status of hydration. From *Figure 2* one can estimate the amount of fluid that will

This study was prepared under the guidance and sponsorship of W. J. Kolff, M.D., Head of the Department of Artificial Organs.

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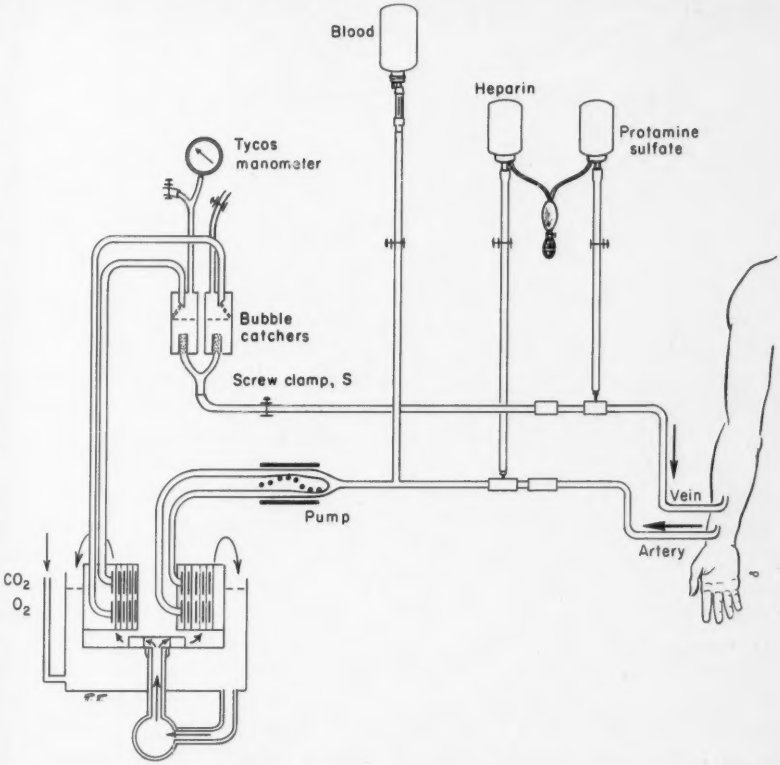

Fig. 1. Schematic drawing of the blood circuit for a twin-coil artificial kidney. The blood comes from an artery or a vein and is pumped into the coils of the artificial kidney. After dialysis the blood proceeds to the bubble catchers, and beyond those a screw clamp, S, regulates the pressure as measured by a Tycos manometer. This pressure determines the degree of ultrafiltration. For so-called regional heparinization, heparin is administered to the arterial line, and protamine sulfate, enough to neutralize the heparin, is administered to the venous line. Thus, the clotting time of the blood in the artificial kidney is prolonged, but the clotting time of the blood in the patient is normal.

be removed from the patient with ultrafiltration. It is important that even with zero pressure in the bubble catchers, approximately 100 ml. of fluid per hour is still removed from the patient during dialysis. The pressure responsible for ultrafiltration is produced by a Sigmamotor pump that is located in the tubing system between the patient and the twin-coil artificial kidney. The patient's blood is pumped into the coil and has to overcome the resistance in the cellophane tubing. Moreover, since the blood flow of 300 ml. per minute is relatively large to

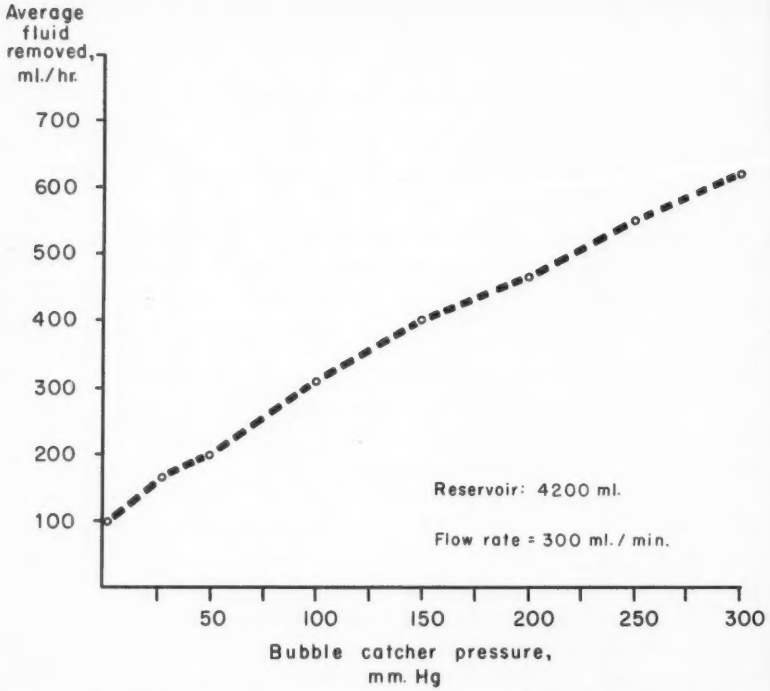

Fig. 2. Plasma water removed when blood was circulated from a calibrated reservoir through a twin-coil artificial kidney, with the usual rinsing fluid on the outside. Only one coil of a twin-coil artificial kidney was used. When the filtration pressure increased as indicated by the pressure measured in the bubble catchers, the amount of fluid removed by utlrafiltration increased from 100 to 600 ml. per hour (it would be more if two coils were used).

be accommodated by the patient's forearm vein, there is usually a resistance to overcome, which will also affect the ultrafiltration. Some patients require replacement of the fluid removed by the unavoidable ultrafiltration, in order to avoid becoming dehydrated during hemodialysis.

In the 35 patients, mentioned before, who required ultrafiltration, clinical improvement was apparent within the first two hours of dialysis, and the removal of body fluid was reflected in a weight loss of from 5 to 12 pounds. Patients who were greatly overhydrated required more than one treatment with a short interval between dialyses.

Illustrative Case Reports

Case 1. A 36-year-old housewife was admitted to the Cleveland Clinic Hospital on the eleventh postpartum day because of acute renal failure that had followed a trans-

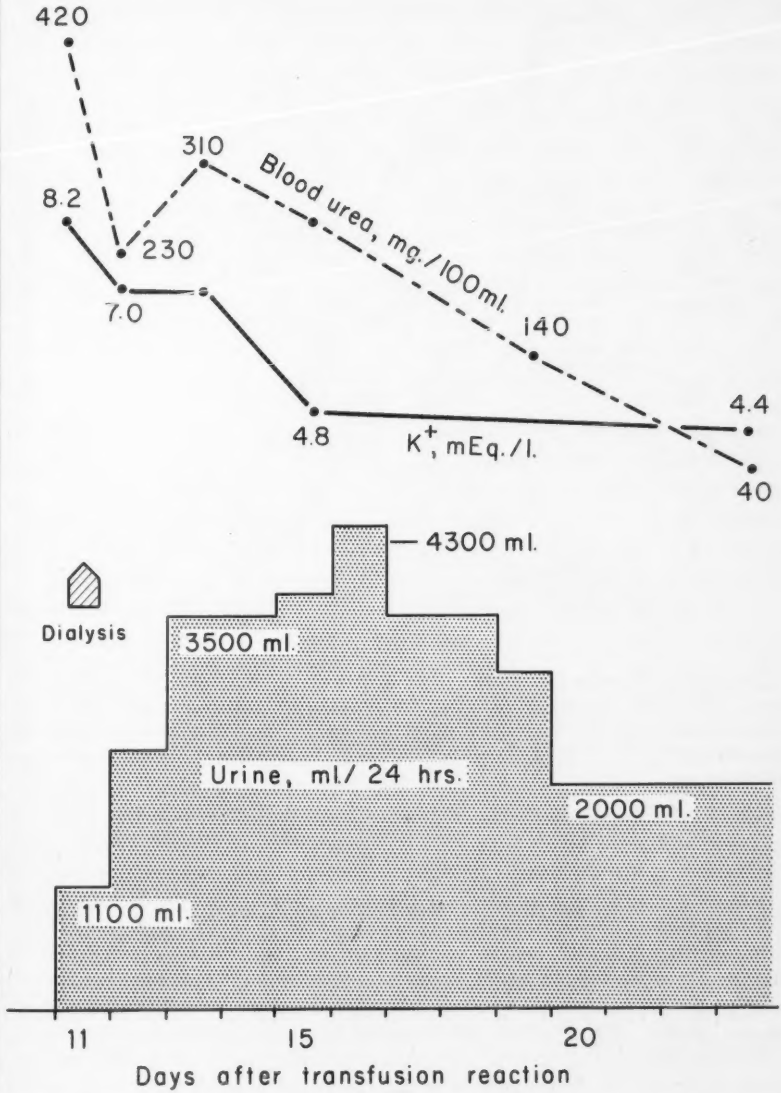

Fig. 3. Case 1. Acute renal failure developed following reaction to a blood transfusion. Graph shows the reduction of blood urea and serum potassium concentrations during dialysis, and the daily urinary output. Most important was the dramatic improvement of pulmonary edema during dialysis and ultrafiltration.

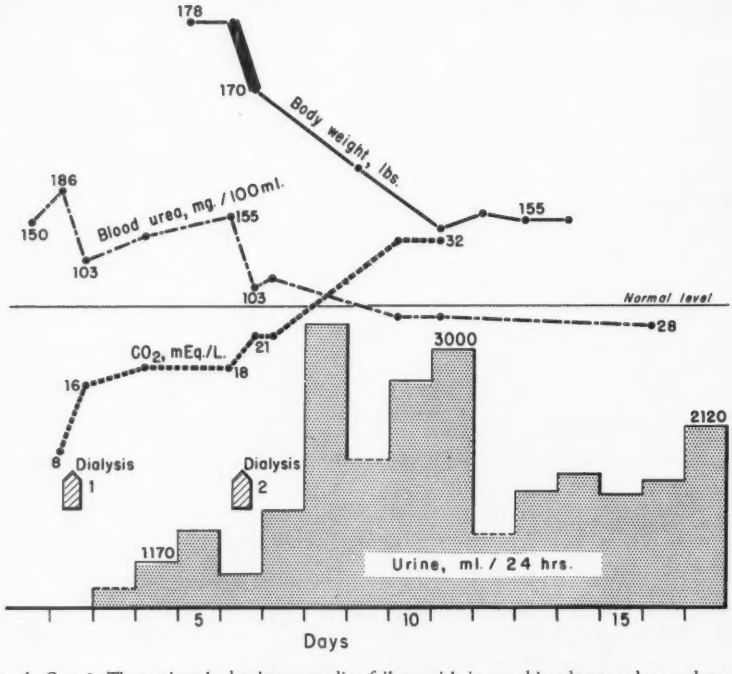

Fig. 4. Case 2. The patient had primary cardiac failure with intractable edema and secondary renal failure. Graph shows the changes, resulting from hemodialysis, in blood urea concentration and plasma carbon dioxide content. Note the reduction in body weight during the second dialysis and ultrafiltration, and the large urinary output thereafter when the patient became responsive to diuretics.

fusion of incompatible blood. The congestive failure and pulmonary edema that developed had been treated with digitalis and oxygen without apparent response. Upon admission here she was severely ill with pulmonary edema and uremia, and she was immediately treated with dialysis and ultrafiltration. Since no compatible blood could be obtained, even after crossmatching more than 40 pints of blood, a single coil of the twin-coil artificial kidney was primed with 6 per cent dextran in 5 per cent dextrose solution instead of with blood. She underwent hemodialysis plus ultrafiltration without complication. Within two hours her clinical condition had improved and the signs of pulmonary edema had disappeared. She recovered from acute renal failure and was discharged 13 days after admission. Because she was critically ill, she was not weighed either before or after dialysis but the improvement of the pulmonary edema showed the effect of ultrafiltration. *Figure 3* shows the decrease in concentration of blood urea and in serum potassium during the dialysis.

Case 2. A 52-year-old man, with a history of angina pectoris and progressive cardiac failure for nine years, was admitted to the Cleveland Clinic Hospital with severe

congestive cardiac failure. Despite intensive medical management, including administration of digitalis and mercurial diuretics, the urinary output decreased to less than 500 ml. per 24 hours; body weight increased rapidly and azotemia developed. He became stuporous and dyspneic with the Kussmaul type of respiration. (Serum carbon dioxide content was 8 mEq. per liter.) So-called "intractable" cardiac edema developed, and his clinical condition rapidly deteriorated. As a last resort on the fifteenth and nineteenth hospital days the patient was treated with hemodialysis and ultrafiltration. As he was severely ill he was not weighed at the time of the first dialysis; however, during the second dialysis he lost 8 pounds in weight. After removal of fluid by ultrafiltration and correction of electrolyte concentration (shown in *Figure 4)* by hemodialysis, he responded to mercurial diuretics. Two days after the second dialysis the urinary output was 3000 ml. per 24 hours. The ensuing hospital course was uncomplicated, and he was discharged 22 days after the second dialysis.

Summary

The artificial kidney has been used successfully in removing edema fluid in overhydrated patients. Up to 600 ml. of fluid can be removed by ultrafiltration alone, and up to 1200 ml. per hour by ultrafiltration and osmosis when dextrose is added up to 10 per cent in the rinsing solution. Two cases are reported of patients who were treated with hemodialysis and ultrafiltration. One of the patients had uremia and pulmonary edema; the pulmonary edema improved within two hours; recovery ensued. The other patient had cardiac failure with "intractable" edema and secondary oliguria; this patient became responsive to diuretics to which he had been unresponsive before dialysis.

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THE ROLE OF THE ARTIFICIAL KIDNEY IN CORRECTING SERUM ELECTROLYTE ABNORMALITIES IN RENAL FAILURE

Report of Four Representative Cases

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Department of Artificial Organs

AT the Cleveland Clinic Hospital, from January 1, 1957, to September 20, 1960, a total of 651 dialyses was performed on 258 patients with either acute or chronic renal failure. The Kolff disposable twin-coil artificial kidney was used. Often, the correction of serum electrolyte abnormalities was either a primary or a secondary reason for initiating dialysis. *Table 1* shows the number of patients in whom the serum electrolyte concentrations were either abnormally high or low before dialysis. The possibility of correcting the electrolyte abnormalities with the artificial kidney is well known. *Table 2* summarizes the results[1,2] of the 64 first dialyses performed for acute renal failure in 1957 and 1958. Serum potassium values were within normal limits after 63 of the 64 dialyses. When serum electrolyte values did not return to within the normal range during the first dialysis, they usually did so, after the second or third dialysis.

Table 1.—*Serum electrolyte data at the onset of 651 dialyses on 258 patients*

Number of determinations	Serum electrolyte	Concentration, mEq./l.
13	Sodium	>145
57	Sodium	<125
26	Potassium	> 7.0
25	Potassium	< 3.5
5	Chloride	>110
150	Chloride	< 90
10	Carbon dioxide content	> 30
238	Carbon dioxide content	< 20

Four representative case reports are presented to illustrate the effectiveness of the disposable twin-coil artificial kidney in correcting electrolyte abnormalities in patients with renal failure. Since each patient had multiple abnormalities in the serum electrolytes, the one or two outstanding deviations are indicated for each case.

This study was prepared under the guidance and sponsorship of W. J. Kolff, M.D., Head of the Department of Artificial Organs.

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Table 2.—*Status of electrolytes in 64 patients with acute renal failure, before and after the first dialysis*

Number of patients with abnormal electrolyte content		Serum electrolyte	Normal range, mEq./l.
Before	After		
24	9	Sodium	130-145
15	1	Potassium	3.5- 5.5
34	3	Chloride	90-110
42	10	Carbon dioxide content	20- 30

Four Representative Case Reports

Case 1. *High serum potassium and low serum carbon dioxide content.* A 15-year-old boy was admitted to the Cleveland Clinic Hospital because of progressive weakness, oliguria, and generalized edema that developed six weeks before admission. For the past year he had a backache and had also lost 40 pounds in weight. Two days after admission he underwent dialysis and ultrafiltration with the twin-coil artificial kidney, and a pronounced improvement occurred in the serum potassium concentration *(Table 3).* Temporary clinical improvement followed, but the glomerulonephritis was beyond recovery, and he died several weeks thereafter.

Case 2. *High serum sodium content.* A 39-year-old woman underwent surgical repair of an interatrial septal defect that had been symptomatic for many years. The postoperative course was normal for five days, and then a fever developed, also generalized edema, oliguria, and signs of toxic psychosis. The cause of distress or renal failure was never explained. The patient had no history of renal disease, hypertension, or other predisposing factors. To control the fever, she was placed under artificial hibernation,[3] and to reduce the edema and the high serum sodium content, she was treated with a three-hour dialysis with ultrafiltration. The only explanation for the high serum sodium content may be that dextrose was administered in saline solution instead of in water. The electrolyte concentrations before and after dialysis are listed in *Table 3.* The most remarkable change was the lowering of the serum sodium content; in a patient who is both overhydrated and anuric, it can be accomplished only by dialysis. Diuresis ensued several days after dialysis; by then, the electrolyte values were within normal limits, and her mental condition was greatly improved. The patient was discharged from the hospital and she is now in excellent health.

Case 3. *Low serum sodium and low serum chloride content in the presence of edema.* A 40-year-old man was admitted to the hospital in acute distress. He had a long history of chronic renal insufficiency associated with hypertension, anemia, and azotemia. On the day of admission he underwent dialysis and ultrafiltration with the twin-coil artificial kidney.

After dialysis, an immediate increase occurred in the serum sodium and the serum chloride concentrations *(Table 3)*. If correction of the electrolyte abnormality had been attempted without dialysis and ultrafiltration, cardiac failure and pulmonary edema would certainly have resulted. After dialysis his clinical condition improved considerably, although oliguria persisted. To stabilize improvement, he was given four more dialyses before he was discharged, and then 14 additional dialyses on an outpatient basis (through a Teflon arteriovenous shunt fastened in his arm). He was able to engage in most normal activities; the daily urinary output never exceeded 200 ml. The electrolyte values remained within normal limits. Approximately six weeks after his discharge he died suddenly of cardiac failure and pulmonary edema.

Case 4. *Low serum potassium and low serum carbon dioxide content.* A 30-year-old man was admitted to the hospital in a coma. Twelve years before admission he had been in an automobile accident and had sustained a ruptured bladder for which he underwent a suprapubic cystostomy and later a ureterosigmoid anastomosis. Subsequently, urinary tract infections developed and, in addition, chronic renal insufficiency. Two months before entering the hospital he had back pain, vomiting, weakness, and a low-grade fever. Upon admission to the Cleveland Clinic Hospital, he was comatose, febrile, and acidotic. He underwent dialysis for six hours with the twin-coil artificial kidney. The serum electrolyte values before and after dialysis are shown in *Table 3*. These values remained normal throughout his hospital course, but the fever, because of staphylococcal septicemia and multiple abscesses throughout the body, resisted all therapy, and he died nine days after admission.

Table 3.—*Correction of serum electrolyte values; values before and after the first dialysis on four patients (cases 1-4)*

Serum or plasma determination	First dialysis							
	Case 1		Case 2		Case 3		Case 4	
	Before	After	Before	After	Before	After	Before	After
Sodium, mEq./l.	140	136	172	148	115	129	127	127
Potassium, mEq./l.	9.0	4.5	4.1	4.2	4.5	3.9	2.9	4.6
Magnesium, mEq./l.	—	—	—	—	—	—	1.9	2.5
Chloride, mEq./l.	101	100	133	108	54	83	93	94
Phosphorus, mg./100 ml.	—	—	—	—	18.9	8.5	—	—
Carbon dioxide content, mEq./l.	7.4	17.2	19.5	18.9	18.9	25.9	11	18
Creatinine, mg./100 ml.	22.2	12.7	—	—	23.6	2.2	1.8	1.0
Blood urea, mg./100 ml.	420	220	143	95	—	—	—	—

Conclusion

Six hundred fifty-one treatments with the twin-coil artificial kidney were performed on 258 patients at the Cleveland Clinic Hospital from January 1, 1957, to September 20, 1960. Severe electrolyte disturbances were present before dialysis in nearly one half of the cases. The twin-coil artificial kidney is an effective means of correcting abnormalities of serum electrolytes, whether the values are too high or too low before dialysis.

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ARTIFICIAL HIBERNATION

Report of Three Cases Including Two with Dialysis

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ARTIFICIAL hibernation has been used at the Cleveland Clinic Hospital only as a last resort in the treatment of extremely ill patients. Its status is that of adjunctive, not specific, therapy. In 1955, Kolff[1] reported nine patients in whom the chief indications for hibernation were hyperpyrexia, uncontrollable deterioration, uncontrollable fall in blood pressure, ileus with severe distention, convulsions, extreme restlessness, coma, and cyanosis. After artificial hibernation, beneficial effects were evident, though there were no long-term survivors. Black and Kolff[2] recently reported the cases of two patients whose recovery was helped by hibernation. A gratifying result in one patient was the cessation of gastrointestinal hemorrhage from a stress ulcer.

This study presents reports of three additional patients, in order to illustrate the current use of artificial hibernation. Two of the patients were also treated with hemodialysis. Because it has been described in detail previously,[1,2] the technic, which is based on that of Laborit, Huguenard, and others,[3] will not be discussed.

Case Reports

Case 1. A 58-year-old man‡ underwent operation at the Cleveland Clinic Hospital for removal of a large substernal nodular goiter and a left carotid body tumor. Insertion of a left internal carotid artery (freeze-dried) homograft was required. Postoperatively, the patient had right flaccid hemiplegia and remained comatose. The endotracheal tube that had been inserted at the time of operation had to be left in place. In the hope of preventing further brain damage, artificial hibernation was instituted in the recovery room by maintaining the rectal temperature between 86 and 93 F. with icebags and a water-cooled mattress while preventing shivering with lytic cocktails[1,2] (meperidine hydrochloride, chlorpromazine, and promethazine hydrochloride). Chloramphenicol was administered prophylactically. The blood pressure was supported with 6 per cent dextran and *l*-norepinephrine bitartrate, and a hydrocortisone preparation was administered on one occasion. *Figure 1* shows the progression of vital signs and urinary output.

This study was prepared under the guidance and sponsorship of W. J. Kolff, M.D., Head of the Department of Artificial Organs.

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‡*This patient was treated in collaboration with Dr. George Crile, Jr., Department of General Surgery.*

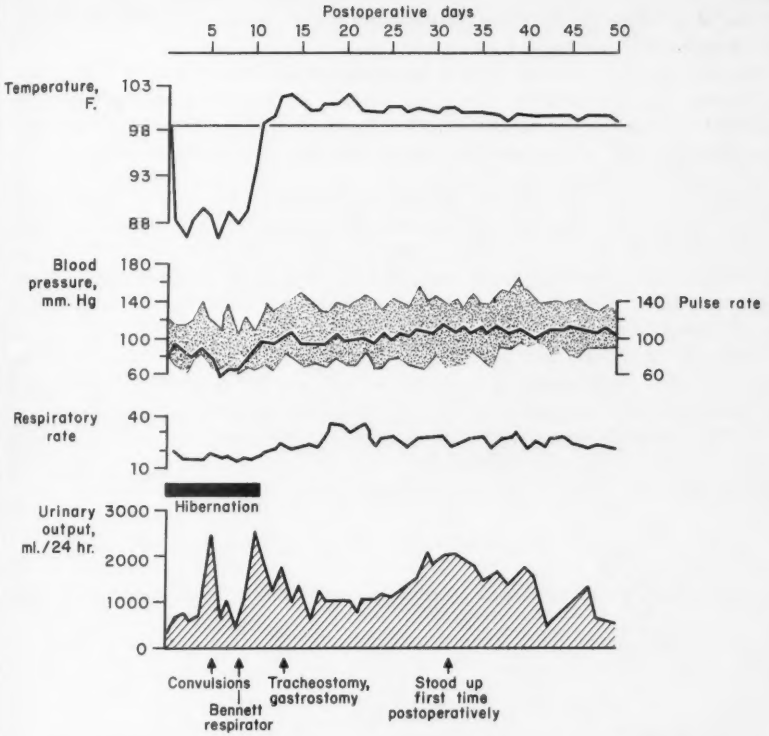

Fig. 1. Case 1. Artificial hibernation was started in the evening after surgery. The lowest temperature was 86 F. On the fifth day, convulsions occurred and papilledema was observed; diphenylhydantoin sodium was administered. A Bennett respirator was employed when the blood pH was 7.28 and the serum carbon dioxide was 32 mEq. per liter. Rewarming was accomplished during the ninth and tenth postoperative days.

On the fifth postoperative day, convulsions and papilledema were observed, and diphenylhydantoin sodium was administered. A Bennett respirator was used to correct respiratory acidosis (blood pH, 7.28, serum carbon dioxide content, 32 mEq. per liter). On the ninth postoperative day, rewarming to 95 F., and to 98 F. on the tenth day ended the artificial hibernation. Three days later a tracheostomy and a feeding gastrostomy were performed under local anesthesia.

Except for a morbilliform rash, a febrile episode (probably due to pneumonitis), and minimal bleeding from the gastrostomy, the patient gradually improved. He became more responsive, although aphasic, and finally was able to stand up for the first time 31 days after operation. Within two weeks the urethral catheter, tracheostomy tube, and gastrostomy tube were removed. On the fiftieth postoperative day the patient

was discharged from the hospital. He could ambulate with a cane, feed himself, partially dress himself, and speak a few words.

Comment. It was hoped that artificial hibernation would lessen the brain damage that had occurred after the clamping of the left carotid artery during the operation. The subsequent recovery of the patient indicated that artificial hibernation may have been a useful adjunct, but it is impossible to assess fully the value of this treatment.

Case 2. A 30-year-old man was admitted to the hospital in a stupor. Twelve years prior to admission he was in an automobile accident and sustained injuries that included a ruptured bladder. To provide urinary drainage, several operations were performed at another hospital: suprapubic cystostomy, left nephrostomy, and finally bilateral ureterosigmoidostomies. Also, calculi were removed from the left kidney. These operations were followed by repeated attacks of pyelonephritis.

When first examined here, the rectal temperature was 105 F.; pulse rate, 160; respiratory rate, 132; and blood pressure, 100/60 mm. of Hg. He appeared pale, emaciated and dehydrated, and had nuchal rigidity, nystagmus, and generalized muscular fasciculations. The laboratory findings were: blood hemoglobin, 9.6 gm. per 100 ml.; blood cell volume, 30 ml. per 100 ml.; white cell count, 17,000 per cubic millimeter. Other data are summarized in *Table 1.* There was moderate uremia and severe acidosis.

Table 1.—*Changes in blood urea and serum electrolyte concentrations (case 2)*

Laboratory findings	Hospital day									
	1									
	Hemodialysis									
	Before	After	2	3	4	5	6	7	8	9
Blood urea, mg./100 ml.	129	52	97	117	—	66	—	94	—	—
Serum sodium, mEq./l.	127	127	132	132	132	134	—	148	—	146
Serum potassium, mEq./l.	3.0	4.6	3.8	4.6	4.6	4.9	—	5.1	—	3.9
Serum chloride, mEq./l.	93	94	96	—	—	—	—	114	—	113
Serum/carbon dioxide content, mEq./l.	11.2	18	17.2	—	—	—	—	18.9	—	15.1

Immediate hemodialysis with the artificial kidney improved his general condition, and further investigation was undertaken. The spinal fluid pressure was 164 mm. of water, and a specimen of fluid was cloudy with many white cells, but no organisms. The culture remained sterile. Penicillin and sulfadiazine were administered intravenously, and streptomycin was injected intramuscularly.

On the third hospital day, seizures developed and the patient lost consciousness. Coagulase-positive *Staphylococcus aureus* was cultured from the blood on two occassions. Administration of streptomycin and sulfadiazine was discontinued since the blood sulfa

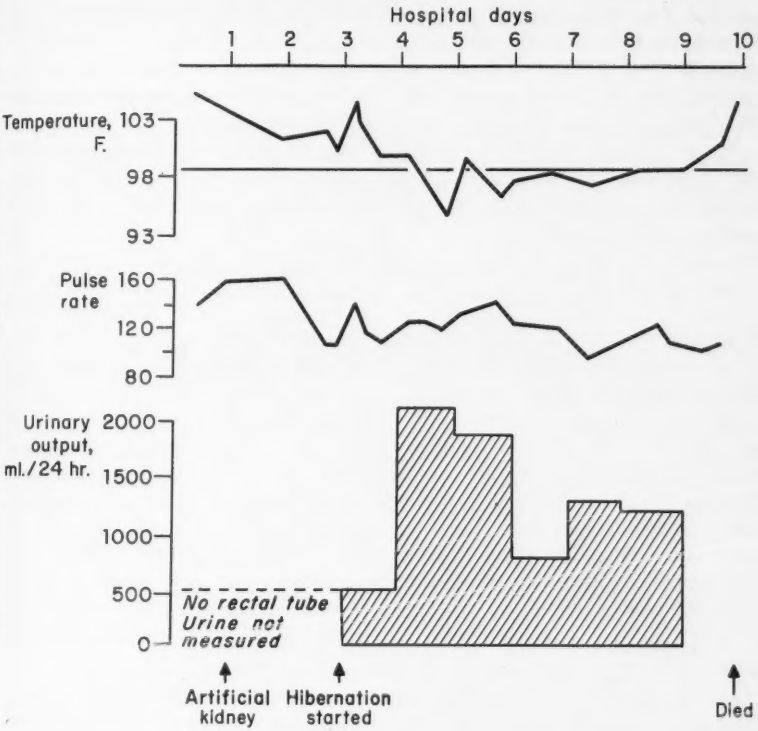

Fig. 2. Case 2. Artificial hibernation was started on the third hospital day because of septicemia and hyperpyrexia. The temperature was reduced to 95 F. in 48 hours, and the pulse rate was decreased. The patient improved temporarily, but treatment was unsuccessful and he died on the tenth hospital day.

concentration was 32 mg. per 100 ml.; chloramphenicol was administered. Since his clinical condition was unquestionably out of control and the course was rapidly deteriorating, artificial hibernation was instituted that day with the use of ice packs, chlorpromazine hydrochloride, and promethazine hydrochloride. The temperature was reduced from 104 to 100 F. in 24 hours, and to 95 F. in 48 hours. The temperature was then maintained at about 98 F. for six days (ninth hospital day). *Figure 2* shows the course of the temperature, pulse rate, and urinary output.

Improvement in his responsiveness and the ability to take some fluid by mouth were encouraging changes. Nevertheless, his condition deteriorated later with the development of conjunctival petechiae, systolic cardiac murmur, disappearance of left popliteal and ankle pulses, decrease of urinary output as measured by an indwelling rectal tube, increase of blood urea content, severe anemia, and decrease in the number

of blood platelets. Intravenous administration of novobiocin and low-molecular dextran, left lumbar sympathetic block, and transfusion of packed blood cells could not reverse the situation. He died on the tenth hospital day, in stupor, having a spiking fever, generalized ecchymoses, and hypotension.

The autopsy revealed the presence of bilateral ureterosigmoidostomies; chronic pyelonephritis; coagulase-positive staphylococcus (blood culture); acute bacterial endocarditis; vegetative aortic valvulitis; multiple myocardial abscesses; cerebellar abscesses; emboli to the spleen, right kidney, and left lower extremity; active duodenal ulcer; and hypoplastic adrenal cortex.

Comment. This patient was moribund when transferred from another hospital. Dialysis with the artificial kidney and artificial hibernation helped to extend his life.

Case 3. A 39-year-old woman* underwent open-heart surgery with the disc oxygenator, for the repair of a large interatrial septal defect. Her recovery was satisfactory except for fever until the fifth postoperative day when an acute schizophrenic episode occurred. Chlorpromazine, 100 mg. every six hours, was administered, and she became depressed and occasionally even catatonic. Roentgenograms of the chest showed evidence of clearing of atelectasis, but the temperature remained between 100 and 101 F. A brief episode of atrial fibrillation occurred, which converted spontaneously to sinus rhythm. On the eleventh postoperative day, administration of chlorpromazine was discontinued because of slurred speech and cogwheel rigidity of the arms. The persistent unexplained fever was now accompanied by hyperactivity. Chloramphenicol was administered, then prednisone for three days, since it had been useful in other patients who had unexplained fever (commissurotomy syndrome or "pump fever") after open-heart surgery.

Clinically, the picture changed from acute psychosis to toxic delirium with progressively elevated temperature and leukocytosis. There was no apparent site of infection, and the neurologic examination revealed nothing abnormal. A chest roentgenogram was normal; blood cultures were sterile; and spinal fluid was normal. A urine culture contained *Proteus vulgaris,* but urinary symptoms were absent. Empirically, erythromycin and chloramphenicol, then penicillin and chloramphenicol were given in large doses.

On the twenty-second postoperative day, laboratory studies revealed that serum sodium concentration was 166 mEq. per liter; serum postassium, 4.1 mEq. per liter; serum chloride, 133 mEq. per liter; serum carbon dioxide content, 19.5 mEq. per liter; blood urea, 143 mg. per 100 ml.; hemoglobin, 14.3 gm. per 100 ml.; cell volume, 40 ml. per 100 ml.; white cell count, 20,800 per cubic millimeter. The next day, dialysis with the artificial kidney was performed and artificial hibernation was instituted; the temperature declined to 94 F. *Figure 3* shows the course of the vital signs and the urinary output. In spite of a large urinary output, the blood urea concentration was 252 mg. per 100 ml. on the twenty-seventh postoperative day. The body temperature was allowed to return to 98 F., and artificial hibernation was discontinued after five days. The patient's mental condition improved, although she was still depressed.

**This patient was treated in collaboration with Dr. Donald B. Effler, Department of Thoracic Surgery.*

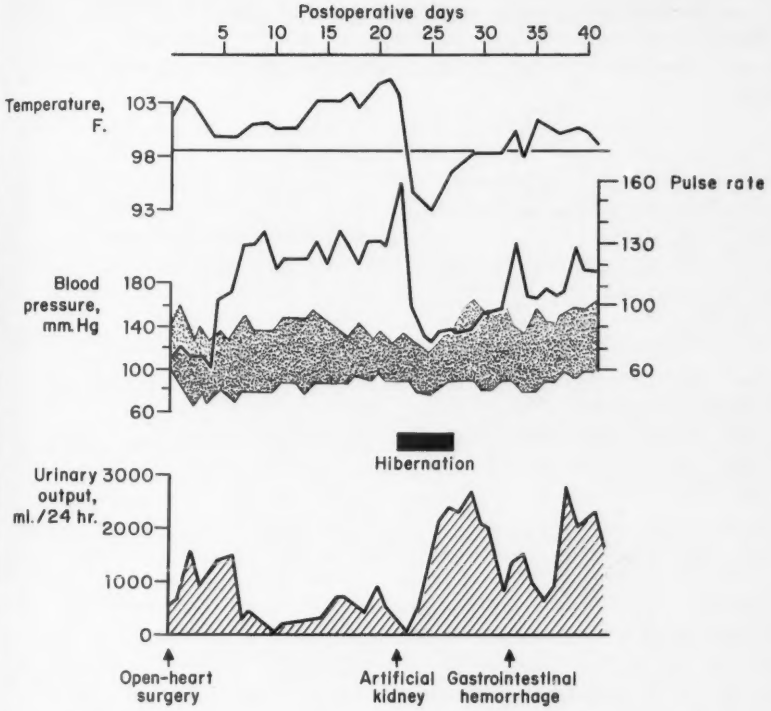

Fig. 3. Case 3. Artificial hibernation was administered after treatment with the artificial kidney on the twenty-third postoperative day. The temperature was reduced to 93 F. and the pulse rate was also reduced significantly. After cooling was discontinued, the temperature and the pulse rate remained normal until gastrointestinal hemorrhage occurred on the thirty-third postoperative day.

The blood urea content decreased to 47 mg. per 100 ml. by the thirty-third postoperative day. Then, when an upper gastrointestinal hemorrhage occurred, the patient received a transfusion of 1500 ml. of whole blood. Medical management for peptic ulcer was instituted. For the first time since artificial hibernation, fever recurred and lasted one week. Proctoscopic examination and gastrointestinal roentgenograms revealed no evidence of a lesion.

Without further incident the patient gradually improved both mentally and physically. Blood urea values returned to normal. Throughout the entire postoperative period the preoperative murmur was absent and the chest roentgenograms showed evidence of a decrease in cardiac size. Fifty days after operation she was well enough to return home.

Comment. This bizarre postoperative course reached a peak with delirium, fever, leukocytosis, and electrolyte imbalance. Despite the fact that a satisfactory explanation was never obtained, treatment with the artificial kidney and artificial hibernation helped recovery.

Summary

Three cases have been presented in which artificial hibernation was used. In two patients the artificial kidney was also employed. Although one patient died, artificial hibernation was thought to be beneficial in cerebral infarction, hyperpyrexia, septicemia, and in a complex of postoperative problems including unexplained pyrexia and delirium.

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DIALYSIS IN THE AGED

Study of Patients Sixty Years of Age or Older

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CLINICAL judgment often interdicts hemodialysis in a patient more than 60 years of age even though the clinical condition might be greatly improved for some time by this procedure. In our experience, hemodialysis has proved to be of considerable benefit in this age group if the renal lesion itself is not accompanied by a fatal condition elsewhere in the body. This report describes the results of dialysis in 41 patients 60 years of age or older who were treated during the three-year period of January 1, 1957 through December 31, 1959.

The over-all management of these patients, in addition to hemodialysis, included control of fluid and electrolyte balance, close medical observation, and administration of drugs.

According to the type of renal insufficiency, these patients were divided into two groups, *acute uremia* and *chronic uremia (Table 1)*. Each of these was then divided into two subgroups designated *survival* and *death*. For the purpose of this study, survival in acute renal failure indicates return of adequate renal function; survival in chronic renal failure indicates improvement sufficient to sustain life for two months after the first dialysis. Also, for this analysis we have divided the group of patients who died, into two subgroups designated as potentially *recoverable* and *irrecoverable*. We have considered renal insufficiency as an irrecoverable condition only when it accompanied an incurable and fatal illness such

Table 1.—*Grouping of 41 patients 60 years of age or older who underwent dialysis in the period from 1957 through 1959*

Status after dialysis	Number of patients	
	Acute uremia (29)	Chronic uremia (12)
Survival	9	4
Death	20	8
Potentially recoverable	3	2
Irrecoverable	17	6

This study was prepared under the guidance and sponsorship of W. J. Kolff, M.D., Head of the Department of Artificial Organs.

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as ruptured aortic aneurysm, major cerebrovascular accident, carcinoma, fatal myocardial infarction, massive pulmonary embolism, or severe pulmonary insufficiency due to overwhelming acute bronchopneumonia. The basis for this classification is from our experience and that of Scribner and associates,[1] that chronic renal failure can be controlled for many months by repeated dialyses, and, therefore, that it need not be an immediately fatal illness even though renal function itself cannot support life.

Acute Uremia

There were 29 patients with acute uremia; 17 were irrecoverable. Of the 12 potentially recoverable patients, nine survived. Three potentially recoverable patients died of pneumonia, severe heart disease, or massive gastrointestinal bleeding. It is impressive that in this small series of 29 patients, acute uremia developed in 13 patients postoperatively, particularly after corrective vascular surgery. There were eight patients who had had vascular surgery; five had such extensive extrarenal disease as to be irrecoverable; of the three potentially recoverable patients, one actually recovered. In comparison, of the 21 other patients in the acute uremia group, of nine potentially recoverable patients eight survived.

Chronic Uremia

There were 12 patients with chronic uremia; six were irrecoverable. Six were potentially recoverable; four survived. Of the two potentially recoverable patients who died, one had pulmonary edema with paralytic ileus and the other had chronic pyelonephritis that was inadequately treated. (Treatment was abandoned in the latter case when it was found the patient had chronic renal disease.)

Precipitating Incidents

A definite incident precipitated the need of hemodialysis in many patients in this study. It is apparent from *Table 2* that infection and surgical procedures were the predominant precipitating incidents. Protracted surgical procedures, particularly corrective vascular surgery, carry great risks in this group. In other patients, the chronic uremic state was accelerated by the occurrence of protracted nausea and vomiting.

Discussion

The case histories reviewed here are of patients treated during a period when indication for dialysis in acute renal failure was not so clearly defined as now, and when dialysis in patients with chronic uremia was considered unwise. Since early 1960, it has been the practice here to dialyze the patients who have acute or chronic renal failure, as often as is needed to keep them symptom-free and in nearly normal electrolyte balance. Currently, survival in unselected patients with

Table 2.—*Incidents precipitating renal failure requiring hemodialysis in 38 patients 60 years of age or older*

Precipitating incident	Number of patients			
	Acute uremia		Chronic uremia	
	Survival	Death	Survival	Death
Surgery	3	10	—	5
Infection	1	5	—	2
Hepatorenal syndrome	—	2	—	—
Renal calculus	—	—	1	—
Exacerbation of lupus erythematosus disseminatus	—	—	1	—
Other	5*	3†	—	—

*Carbon tetrachloride poisoning, burns, transfusion reaction, trauma, carcinoma.
†Carcinoma, congestive cardiac failure, constrictive pericarditis.

chronic renal failure has consistently been longer than two months beyond the first dialysis among those patients who receive succeeding hemodialyses and who follow the prescribed medical management. Although these patients have been less than 60 years of age, there is no reason to believe that similar results would not be obtained in patients 60 years of age or older.

Conclusion

From the analysis of 41 cases it is possible to conclude that advanced age alone does not contraindicate dialysis, and that the survival rate is high in potentially recoverable patients. Of 12 patients with potentially recoverable acute uremia, nine recovered; and of six patients with potentially recoverable chronic uremia, four recovered. Since a true judgment of recoverability often can only be established through necropsy, hemodialysis should not be withheld from the elderly patient unless there is unquestionable evidence that survival is not possible. Acute renal failure resulting from acute tubular necrosis is still amenable to management (which includes exacting medical care as well as hemodialysis) and leads to recovery despite advanced age. Aged patients with chronic renal failure also can be helped with hemodialysis.

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LABORATORY AIDS IN THE DIAGNOSIS AND TREATMENT OF URINARY TRACT INFECTIONS

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PYELONEPHRITIS and related infections of the urinary tract are among the most frequently undiagnosed and most difficult to manage of all infectious diseases. A few selected data will indicate the magnitude of this problem: (1) pyelonephritis is the commonest renal lesion found at autopsies, and has been reported in up to 20 per cent of consecutive necropsies;[1,2] (2) the clinical diagnosis of urinary tract infection had been made in only 20 per cent of those patients who at necropsy were found to have active pyelonephritis, and the diagnosis is missed equally often whether massive or minimal lesions are present.[2] This disparity between clinical diagnosis and autopsy findings indicates that overt clinical symptoms of pyelonephritis are frequently absent.

The natural course of pyelonephritis has been described as a series of separate episodes of infection. Now, evidence suggests that pyelonephritis is a disease continuum, and in many cases the episodes of acute infection are linked by an asymptomatic but active infection that is constantly taking its toll on renal function.[3] The initial event in the relentless course of chronic pyelonephritis may occur during childhood. Macaulay and Sutton,[4] as well as others,[5,6] reported that chronic infection developed in from 30 to 60 per cent of children who had urinary tract infection in childhood. The recent studies by Kass[7] on the occurrence of true bacilluria (100,000 or more organisms per milliliter of urine) in asymptomatic patients have shown a high incidence of asymptomatic pyelonephritis in the general population.

It becomes readily apparent that one cannot depend on typical symptoms and signs alone to make the diagnosis of pyelonephritis. The purpose of this paper is to review briefly the pathogenesis and factors that influence the course of pyelonephritis and to present the laboratory methods that may be of some value in the diagnosis and treatment of pyelonephritis.

Pathogenesis

Major gaps exist in our knowledge of the pathogenesis of pyelonephritis. We do know that bacteria may reach the kidneys by four possible routes; some experimental evidence as well as clinical data supports this knowledge.[8]

1. *Hematogenous route.* There is little question that coccal infections of the kidney result from hematogenous involvement from a primary focus such as a caruncle. It is unlikely, however, that organisms from the intestinal tract enter the blood stream and lodge in the kidneys, because coliform organisms are rarely found on blood cultures, and one must wonder why only the renal parenchyma

would be involved. Bacteremia is frequently associated with instrumentation on the lower urinary tract,[9] and may initiate renal infection, particularly when the kidney has been damaged either by pre-existing parenchymal disease or some type of obstructive uropathy.

Experimental pyelonephritis may be produced in the laboratory animal by massaging the kidney and then injecting organisms intravenously.[10] Similar infections have been produced in the partially obstructed kidney.[11] Recently, Guze, Goldner, Finegold, and Hewitt[12] reported the production of pyelonephritis in unobstructed kidneys in rats, using *Streptococcus faecalis.* This finding in the experimental animal would lend credence to the belief that in man the hematogenous spread of organisms can produce pyelonephritis in normal kidneys if a sufficient number of bacteria localize therein.

2. *Ascending route.* Contamination of the bladder by organisms entering through the urethrae undoubtedly occurs, particularly in females, who have short urethrae. Upper urinary tract infection may occur by way of ureterovesical reflux secondary to inflammatory changes at the ureterovesical junction, or because of obstruction at the outlet of the bladder, which thereby necessitates increased intravesical pressure in voiding. Recently, Vivalde, Cotran, Zangwill, and Kass[13] produced in rats the experimental prototype of this route of infection; they used a strain of *Proteus vulgaris.*

3. *Lymphogenous route.* There are no well-defined direct lymphatic connections between the colon and the kidneys.[14] Lymphatic drainage of the ureter is segmental, and whether bacteria may or may not ascend via the lymphatics from the bladder to the kidneys is not known. Recently, Murphy[15] placed carbon particles in the bladders of dogs and studied the migration of these particles at various levels of intravesical pressure. He found that if the intravesical pressure remained at 40 cm. of water, the carbon particles remained in the bladder; but, if it was increased to 70 cm., carbon particles were seen in the periureteral tissues and in the lymph nodes around the renal pelvis.

4. *Direct extension.* Direct extension of infection to the kidneys from surrounding inflammatory tissue undoubtedly occurs, but probably only rarely and does not play a significant role in the pathogenesis of pyelonephritis.

Factors That Influence the Course of Pyelonephritis

Specific nephrogenicity of bacteria. Little is known about the specific nephrogenicity of certain bacterial strains but, knowing that in nearly all types of infection there are strains of high and low virulence, it is thought that this principle may apply to bacteria that enter the urinary tract.

Genetic predisposition. The frequent occurrence of urinary tract infection in children with congenital abnormalities of the urinary tract is well known. Recently, certain microscopic congenital abnormalities were reported,[16] such as congenital immaturity of a nephron and microscopic dysplasia. These abnormal foci may be areas that are particularly susceptible to the infecting organism.

Specific host susceptibility. Host resistance plays an extremely important part in urinary tract infections, as most infections are a delicate balance between states of host resistance and growth of organisms. The presence of potent nonspecific antibacterial substances has been demonstrated in the normal urine.[17] Rowley[18] recently demonstrated that complement fixation may be an important natural inhibitor of bacterial multiplication. The fourth component of the complement is inactivated by ammonia. Since the renal medulla produces ammonia from glutamine, this may explain why the medullary areas of the kidneys are especially susceptible to infection. There is no specific evidence of renal damage due to specific antigen-antibiotic reactions or an autoimmune phenomenon, but in sensitized animals, bacterial endotoxin will produce severe renal lesions.[19]

Functional defects. Certain functional demands placed on the kidneys would seem to increase their susceptibility to infection. The breakdown products of many drugs are excreted by the kidneys, and there is some evidence to suggest that the presence of these products may increase susceptibility to the infecting organism.[20]

Acquired structural defects. The structural changes associated with obstructive uropathy or renal parenchymal disease of an acquired nature predispose the urinary tract to infection.

Laboratory Aids in Diagnosis

The patient with pyelonephritis whom the physician is usually called upon to treat is the one who has overt signs of urinary tract infection such as urgency, frequency, dysuria, pain in the costovertebral angle (with or without chills and fever). The diagnosis in such a case is not difficult to make because unmistakable urinary abnormalities usually are present. An asymptomatic patient with urinary abnormalities presents the greatest problem in diagnosis. In such a case it may be necessary to utilize several laboratory procedures to rule out or to confirm the diagnosis of pyelonephritis.

Urinalysis. The first morning-voided specimen is the best to examine, as it has been in the bladder overnight and any bacteria present will have multiplied.[2] Proteinuria is usually not so severe in pyelonephritis as it is in glomerulonephritis, because there is little initial glomerular damage. Pyuria is frequently present, although recognition of it is not necessary for a diagnosis of pyelonephritis. Pyuria, arbitrarily defined as the presence of more than from 3 to 5 leukocytes per high-power field in the urine, was present in 84 per cent of 253 randomly selected patients with more than 100,000 bacteria per milliliter of urine.[21] In patients with chronic pyelonephritis the incidence of pyuria is between 30 and 50 per cent.[7] Few casts are usually found in the urine, for although the tubules are dilated and filled with colloidal material they are also obstructed, and the casts cannot enter the urine. The gram stain or methylene-blue stain of the urinary sediment, for bacteria, is an extremely valuable diagnostic procedure. It

is usually positive for bacteria when 100,000 or more organisms are present per milliliter of urine;[2] but, unfortunately, an intrinsic error of from 20 to 30 per cent exists even in the most skillful hands.[21] The Addis count is a good tool for quantitating the sediment and may be helpful in some cases in differentiating glomerulonephritis, nephrosclerosis, and pyelonephritis.[22]

Glitter-cell phenomenon. Sternheimer and Malbin[23] developed a special stain (gentian violet-safranin) that facilitates recognition of glitter cells. These cells are polymorphonucleated leukocytes that stain a pale blue and contain granules in the cytoplasm which exhibit Brownian movement. Normal polymorphonucleated leukocytes immersed in a hypotonic solution will become glitter cells, and when returned to isoosmolarity they again become normal. It would seem that the osmolarity of the urine plays a role in the formation of the glitter cell. However, osmolarity is not the only factor in the production of glitter cells, as hypertonic urine may contain them, and it is undoubtedly a combination of hypotonicity and decreased resistance of the leukocyte to changes in osmolarity that produces the characteristic leukocyte.[24] Glitter cells are frequently present in the urine of patients with pyelonephritis, but they may also be seen elsewhere in the urinary tract in inflammatory disease such as prostatitis, so they are not pathognomonic for pyelonephritis. The presence of glitter cells should make one think of pyelonephritis, but their absence should not exclude consideration of this diagnosis.[25]

Griess's test. The majority of organisms producing urinary tract infection will reduce to nitrites the nitrates normally present in the urine. Griess's test will show the presence or absence of such organisms. The Griess agent contains sulfanilic acid, acetic acid, and alpha-naphthylamine. When the agent is added to the urine containing nitrite, it rapidly turns red because of the formation of azo-alpha-aminonaphthaline parabenzine-sulfonic acid. Uninfected urine contains no nitrite and does not change in color. To be reliable, a screening test must be sensitive and must elicit a low incidence of false-positive, and false-negative reactions. The chief drawback with Griess's test is its insensitivity:[26] a significant bacilluria can be present and a Griess's test may be negative.

Urine cultures. In the standard culture of the urine there is always the problem of determining whether or not the organism obtained in the culture is a contaminant or a true pathogen. The introduction of the quantitative urine culture, a technic that has long been in use by the United States Public Health Service for bacterial counts in contaminated water, presents a method by which true bacilluria can be differentiated from contamination.[27]

The technic is roughly as follows: a 1-ml. specimen of urine is appropriately diluted (depending on the number of organisms counted on the stained sediment) and is incorporated into a pour plate of 9 ml. (or more depending upon the dilution) of a general culture medium such as trypticase soy agar. After 24-hour incubation the colonies are counted and, assuming that each organism is viable and produces a colony, a quantitative estimation of the number of bacteria per

milliliter of urine is calculated. In careful studies it has been found that significant bacilluria is present when 100,000 or more bacteria are found in 1 milliliter of urine. When less than 1,000 organisms per milliliter of urine are present, they are contaminants; organisms present in the range from 1,000 to 10,000 per milliliter are of variable significance.[7] Certain limitations must be recognized, for even in the presence of severe pyelonephritis, bacterial counts less than 100,000 per milliliter of urine may be obtained if: (1) a bacteriostatic agent is in the urine; (2) the patient is in the midst of a water diuresis; (3) the discharge of bacteria into the urine from the kidneys is small in number and multiplication in the bladder has not had time to take place; and (4) there is obstruction of the ureters and no organisms enter the urine in the bladder.

Antibody-hemagglutination response. The diagnosis of specific infectious diseases (not in the urinary tract) has been accomplished by the identification of antibody titers against the etiologic agent. This method has not been successfully used in urinary tract infections either because the antibodies were not formed or the methods used were not sensitive enough to register the antibody response. Erythrocytes modified by bacterial antigens are more sensitive agents for the detection of bacterial antibodies than is the standard agglutination test. The antibody-hemagglutination method has been used in patients with urinary tract infections with some success. Erythrocytes from the patient are mixed with a dilution of a specially prepared bacterial antigen which is adsorbed on the erythrocyte. Then the hemagglutination test is performed, using the patient's serum at various dilutions from which the antibody titer is obtained. The technic may be useful in urinary tract infections to identify the specific antibodies isolated on cultures, thus confirming the pathogenicity; and also in subsequent antibody titers to evaluate the effectiveness of therapy.[28]

Needle biopsy of the kidney. Although pyelonephritis is frequently due to a focal lesion and sometimes does not involve the entire kidney, valuable information may be obtained by biopsy of the kidney with the Vim-Silverman needle. At the time the renal biopsy specimen is obtained, a culture is also made from the needle. This technic may be extremely useful in selected patients.[29]

Laboratory Aids in Treatment

The key to successful therapy of pyelonephritis is the selection of the appropriate antimicrobial agent. It is well at this time to review the various methods of determining in vitro sensitivity, and the reliability of the tests in determining in vivo effectiveness.[30,31]

The agar diffusion method of determining sensitivity consists of placing an antibiotic-impregnated disk on the surface of an agar plate cultured with the specific microorganisms. The antibiotic diffuses over the surface of the plate, and the size of the clear zone surrounding the organic colony is used as a measure of the inhibitory power of the antibiotic being tested. The individual disks contain various concentrations of the antibiotic, registering various degrees of sensitivity.

The chief drawback of this method is the inaccuracy that is largely due to a failure to standardize the concentration of antibiotics in the disk. Moreover, the matrix in which the antibiotic is contained has variable binding and releasing properties, so that diffusion is not uniformly even. There is a great need to standardize these disks, and Branch, Starkey, and Power[32] are working toward this goal.

The agar dilution method involves the use of various concentrations of antibiotics that are incorporated into pour plates. Several organisms can then be tested on one plate. This method is accurate but, unfortunately, is cumbersome and therefore not in widespread use.[33]

The tube dilution method utilizes a series of tubes containing various dilutions of antibiotics in a broth medium. The tubes are inoculated and incubated for a 24-hour period. A lack of growth is indicated by absence of turbidity. This is by far the most accurate method at the present time to determine sensitivity of a patient to various antibiotics.

The rapid hemoglobin-reduction method[34] of determining sensitivity is a technic that consists of seeding the organisms in a tube of melted and cooled brain-heart infusion agar plus dextrose. This solution is poured into Petri dishes containing a thin layer of heart infusion plus 20 per cent citrated blood. Impregnated disks are placed on the surface and the preparation is incubated. Prior to the appearance of visible growth, most pathogenic strains of organisms will develop relatively intense reducing conditions within the medium, which are reflected in the reduction of the hemoglobin and therefrom a change in the color of the blood. Inhibition of growth causes no change in color of the blood, and zones of inhibition are therefore identifiable. Results are available in from two to four hours after inoculation.

There are many factors present in vivo that influence the effectiveness of antibiotics: (1) the rapidity with which the bacterial population multiplies; (2) the physical and chemical natures of the environment in which the organisms live, because blood, exudate, and other tissue fluids affect the drug; (3) the amount of the drug in the area in which the bacteria are located; and (4) the extent of the antimicrobial defenses of the host. In spite of these many factors, a correlation between in vitro sensitivity and in vivo results is surprisingly accurate, particularly in acute, uncomplicated infections, and it becomes progressively less accurate in chronic and complicated infections.[35]

Conclusion

The discrepancy noted—between the incidence of severe pyelonephritis demonstrated at autopsy and that of the antemortem diagnosis of pyelonephritis—suggests the existence of a large number of patients with asymptomatic pyelonephritis. The incidence of this disease and the difficulty with which the diagnosis

is made in these asymptomatic patients clearly indicate that all diagnostic procedures available should be utilized. A brief review of the laboratory aids in the diagnosis and treatment of pyelonephritis is presented, and it is hoped that the utilization of these tests will facilitate the detection of asymptomatic pyelonephritis and assist in the therapy of this important renal disease.

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DIAGNOSIS AND TREATMENT OF THE NARCOLEPSY SYNDROME

Analysis of Seventy-Five Case Records

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THE narcolepsy syndrome is known also as *Gélineau's disease, the Gélineau-Redlich syndrome, paroxysmal sleep,* and *sleep epilepsy.* Because of the comparative rarity of the disease and our lack of understanding of the term *narcolepsy,* we recently had difficulty in diagnosing several cases of the syndrome. This report undertakes to clarify the meaning of the term, to discuss the entity, and to report an analysis of 75 case records of narcoleptics treated at the Cleveland Clinic in the last nine years.

In the past it has been alleged that the sleep of the narcoleptic is paroxysmal in onset.[1] *Hypersomnolence* has frequently been used to describe the condition in which the patient is persistently drowsy without having actual sleeping spells, or in which he falls asleep perhaps only once a day while engaged in some activity. Yoss and Daly[2] recently defined narcolepsy as consisting of four components: (1) narcolepsy proper — "excessive and persistent sleepiness"; (2) cataplexy — muscular weakness induced by emotion; (3) sleep paralysis — transient, benign loss of muscle tone at the beginning or end of sleep; (4) hypnagogic hallucinations — usually vivid auditory or visual hallucinations or illusions occurring during day or night drowsiness, usually with sleep paralysis. We are essentially in agreement with their definition. In our 75 patients, excessive and persistent sleepiness occurred alone or in combination with other symptoms. *Figure 1* illustrates the incidence of the four components of the narcolepsy syndrome in our patients. (1) Narcolepsy (excessive sleepiness) was present in all 75 patients. (2) Cataplectic attacks in combination with other symptoms occurred in 51 patients. (3) Narcolepsy occurred alone in 24 patients. (4) Sleep paralysis with other symptoms was present in 10 patients. (5) Hypnagogic hallucinations with other symptoms occurred in 4 patients. (6) The full tetrad was present in 3 patients.

There were 47 men and 28 women in the series, from 20 to 70 years of age. Three patients stated that some other member of the family had symptoms of the narcolepsy syndrome.

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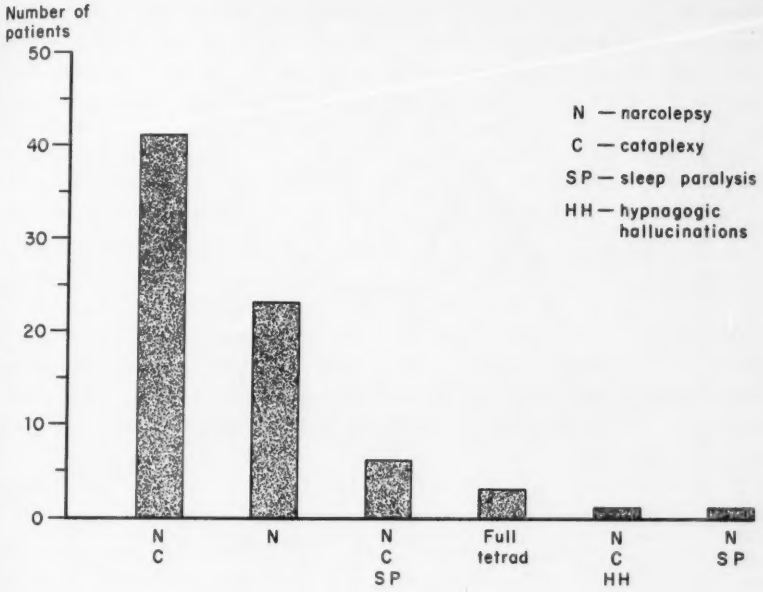

Fig. 1.

Analysis of 75 Case Records

Narcolepsy. The pathognomonic symptom of the syndrome is narcolepsy or excessive and persistent sleepiness. It emerges gradually; however, onset occurred by or before the second decade in 36 patients, and by the third decade in 54 patients *(Fig. 2).* The abnormal sleepiness may be classified on the basis of severity: (1) Constant drowsiness with ability to resist sleep but only at the expense of further drowsiness. (2) Mild sleepiness, rather persistent drowsiness with only rare episodes of sleep. (3) Moderate sleepiness, in which episodes of sleep overtake the person during the usual normal working hours and activities, such as driving, reading, sitting, watching a television program, or at the theater. The patients who fell asleep while driving cars usually were warned in time to stop for a short nap and were not fatigued, although several had serious accidents. (4) Severe sleepiness, episodes of sleep which overtake the person while he is eating, during conversation, while walking, or during situations that usually excite wakefulness, such as watching a baseball game or taking dictation. In 56 patients, onset of sleep occurred during physical activity. In patients with no history of onset of sleep during activity, cataplexy was present.

Patients with narcolepsy apparently suffer from a persistent, though fluctuating impairment of wakefulness; when this impairment is severe there are episodes

Fig. 2.

of great drowsiness or sleep. Only seven patients either were fatigable or felt constantly tired. Sleep came from no apparent cause and occurred at any time and under any circumstance, but most patients were subject to frequent episodes of sleep that were aggravated by conditions that bring on physiologic sleep, of which complete physical relaxation was the most frequent, although monotonous occupation was a frequent conditioning factor.

The onset of acute episodes of sleep ranged in rapidity from a drifting into sleep without warning (though rarely), to a gradual drowsiness that would herald sleep. The duration of the episodes ranged from a few seconds to several hours, but averaged from 10 to 20 minutes. Short episodes usually recurred during the day. Patients generally felt refreshed on waking. The period of night sleep was from 6 to 12 hours with an average of 8 hours of restful sleep. For nine patients night sleep was disturbed by nightmares, partial insomnia, or restlessness at some time during the course of narcolepsy. Three patients reported that sleep talking and somnambulism occurred.

Cataplexy. Cataplexy consists of muscular weakness induced by emotion; it occurred in 50 patients. The act of laughing induced cataplexy in 33 patients. The emotions of anger or surprise were also apt to induce an attack. Muscular

paresis ranged from a subjective sensation of weakness in one group of muscles to complete paralysis causing the patient to sink to the ground without losing consciousness. Only 16 patients fell to the ground and, in general, before most episodes the patients had sufficient warning and could break the fall by grasping some object. The duration of the attack rarely was longer than one minute. Cataplexy occurred as the first symptom in four patients. Narcolepsy and cataplexy generally were simultaneous in onset; however, in one patient episodes of cataplexy first occurred 16 years after the onset of narcolepsy.

Sleep paralysis. Sleep paralysis is a transient, benign loss of muscle tone at the beginning or the end of sleep and usually is associated with a distressingly clear consciousness. Ten patients experienced episodes of paralysis when drowsing off into sleep, or when waking from sleep but while still drowsy. The number of attacks was equally divided, as to correlation with time of sleep — during the day or night, or upon waking in the morning. The paralyses had the same clinical characteristic as cataplexy, usually lasted less than one minute, but in one patient paralysis remained for more than one hour. Paralysis usually was complete, although a few patients were able to open their eyes and one patient was able to utter a few words. The paralysis was flaccid, but frequently the patients described the sensation as that of feeling "stiff." Recovery was spontaneous or induced. Often a light touch from someone else was all that was needed to disrupt the attack; at times vigorous shaking was necessary.

Hypnagogic hallucinations. Hypnagogic hallucinations occurred in four patients, and were associated with either night or day drowsiness. The hallucinations usually occurred with sleep paralysis while going to sleep. They consisted of vivid visual and auditory experiences that were pleasant as often as unpleasant. Some patients re-experienced scenes from "horror movies." One patient remembered hearing her sister say, "Keep smoking and you will stay awake." One patient was overcome by sleep from the sounds of a bell coming closer and closer to him.

Diagnosis

The sole basis for diagnosis is the patient's history, that is, the presence of an excessive and persistent sleepiness. It varies from persistent drowsiness with ability to fight off sleep resulting in more drowsiness, through irresistible single daily attacks of sleep, to frequent episodes of irresistible sleep even while active.

Three other features help in the diagnosis: (1) cataplexy's being associated with narcolepsy in two thirds of the cases and consisting of attacks of muscular paresis rarely lasting longer than one minute and with clear consciousness; (2) sleep paralysis consisting of transient, benign attacks of total absence of voluntary movement at the beginning or end of sleep and usually of short duration; (3) hypnagogic hallucinations consisting of vivid auditory or visual hallucinations, or illusions occurring during day or night drowsiness usually with sleep paralysis.

In three fourths of the patients, sleep came on when they were active, and if the patients did not have narcolepsy associated with activity, they had unmistakable cataplexy.

Differential Diagnosis

Sources of errors. If some of the tetrad of symptoms is absent, or the physician fails to assign significance to the excessive sleepiness, or the patient is unable to describe his abnormality clearly enough to arouse suspicion in the physician's mind, the diagnosis of narcolepsy may be missed.

Anxiety tension states with fatigue. The most common erroneous diagnosis encountered in our series was that of neurotic fatigue. Only eight patients with narcolepsy had associated muscular and physical exhaustion that typifies the neurotic fatigue state. Patients with narcolepsy often sleep from 10 to 15 minutes and awake refreshed, in contrast to the neurotic who naps from two to three hours without obtaining relief of his fatigue. On careful questioning, patients with anxiety and fatigue will state that drowsiness is not present nor are periods of uncontrolled sleep; but some say they need extra sleep because of insomnia at night. When a patient says: "I'm always tired," or "I have no pep or energy," it behooves the physician to determine whether or not the patient has excessive or persistent sleepiness.

Hypothyroidism. The majority of patients with narcolepsy did not state that they had excessive sleepiness, but rather that they had "no pep," or were "tired all the time." These descriptive phrases may inadvertently mask the fact that they mean that they have "excessive sleepiness." When there is doubt as to the meaning, a determination of the basal metabolic rate will aid the clinician. A low rate may substantiate a tentative diagnosis of hypothyroidism. However, such values are not truly accurate, since the patient has not maintained a state of relaxed alertness. The lowered oxygen consumption results from the reduced oxygen requirement associated with the somnolent state and not from a true decrease in the basal metabolic rate. Objective measurements of thyroid function, in narcoleptics, such as the determinations of the protein-bound iodine or the thyroid uptake of radioiodine, have revealed that narcoleptics do not present chemical evidence of hypothyroidism.[2] No patient in our series showed improvement on treatment with thyroid extract.

Obesity. It has been emphasized that obesity as an accompaniment of narcolepsy is additional evidence of an endocrine disorder. In our patients the incidence of obesity in women was no greater than in women in the general population. However, of the 47 men, 15 were 20 per cent or more overweight, and increase in appetite or a gain in weight was not associated with the onset of the disease.

Epilepsy. A diagnosis of epilepsy was under consideration when the patient stated that he *suddenly* fell asleep or blacked out, or when the cataplectic spells were considered akinetic seizures.[3] By careful questioning it was found that all

narcoleptic patients were drowsy preceding their sleeping spells, and were not suddenly overcome with sleep. The patient who mentions blackouts, appears to be a normal person who sleeps with quiet respirations and can be easily aroused by external stimuli. It is not a paroxysmal epileptic unconsciousness from which the patient cannot be aroused. Cataplectic attacks were related to emotional stimuli, and the patients were clearly conscious.

Double vision. Several patients in our series had double vision, thereby arousing suspicions of the presence of myasthenia gravis. Diplopia occurred only with extreme drowsiness. Yoss and Daly[2] stated that patients who had double vision had a relatively high degree of exophoria. The ability to maintain fusion is reduced during drowsiness, thus resulting in latent ocular imbalance and double vision.

Physical and neurologic examination. The results of the examinations were within the normal range and did not aid in establishing the diagnosis of narcolepsy. Lumbar punctures showed no essential abnormalities of the pressure or of the composition of the cerebrospinal fluid. The skull and chest appeared to be essentially normal as shown on roentgenograms. Results of hematologic studies, glucose tolerance tests, blood calcium and phosphorus estimations, serologic tests, and fasting blood sugar values were within normal limits.

Electroencephalograms. Electroencephalograms were recorded for 42 patients, 9 of whom were in the group who had cataplexy, and 33 who had only narcolepsy. Of the 33 patients with narcolepsy, 31 had well-developed background alpha activity except for two patients whose records were obtained mainly while they were asleep. Of the two exceptions, one patient had a background of from 7 to 8 cps. of activity, though well-developed, and the other had a good alpha activity upon hyperventilation for three minutes. According to these records of narcolepsy, 32 patients had what was considered to be excessive amounts of theta slow activity on overbreathing for three minutes. Three of these had both resting and hyperventilation excess in theta slow activity. Of the nine records in the cataplexy group, four showed the presence of excessive slow activity on the resting record or during hyperventilation; the other five records showed that slow activity was normal.

Drowsiness was not studied separately because it could not be dissociated from that caused by the normally used sedatives before recording electroencephalograms. Data in seven records of the narcolepsy group were normal in all respects except for brief runs of moderate amplitude theta activity during the normal background. This was further observed in two of the nine patients in the cataplexy group, both of whom had otherwise normal records. From these observations it is suggested that the electroencephalographic pattern, though not pathognomonic for these conditions, is helpful in that there may be evidence of excessive, slow activity on rest or hyperventilation in about half the patients. In the negative evaluation it would be useful in excluding other neurologic abnormalities from prime consideration even though the diagnosis is made on purely clinical evidence.

Course and Treatment

In our patients, after one episode of narcolepsy the excessive sleepiness persisted relatively unchanged for the duration of the follow-up. Remissions of a few months' duration at the onset were rare. The treatment of narcolepsy is symptomatic and employs the use of agrypnotic drugs. Good results were obtained from dextroamphetamine sulfate,* *d*-Desoxyephedrine hydrochloride,† or amphetamine sulfate.‡ Methylphenidate hydrochloride§ was administered to only a few patients. When a satisfactory regimen was established, 56 of the patients reported excellent relief of excessive sleepiness. Cataplexy was not consistently relieved by agrypnotic drugs, but the attacks were generally reduced in frequency and severity. The reason for this improvement is not clear. Sleep paralysis and hypnagogic hallucinations were not affected by the use of agrypnotic drugs.

Comment

Narcolepsy occurs in patients who are otherwise healthy. Preponderance among men was reported by Daniels;[4] our series is in agreement. However, Yoss and Daly[5] believe that the higher incidence in men than in women may be because men are more apt to seek treatment for the disability because of social economic pressures. In no patient with narcolepsy did signs of epilepsy or organic disease develop, to which the attacks could be attributed. Narcolepsy was not associated with tumors in the brain stem or hypothalamic area; nor did it occur after viral encephalitis, or trauma to the head with prolonged unconsciousness. Although sleep disorders may follow these later diseases, they are distinct from narcolepsy,[6-8] which is an entity in itself. Bradley and Elkes,[9] after a detailed study on the effects of certain drugs on the electric activity of the brain, stated that a slight variation in the local titer of a neurohumoral agent in the midline areas of the reticular formation may profoundly affect the excitability of large neuron pools at great distance. They believe that changes in function may depend on the rate of liberation, diffusion, and destruction of locally produced neurohumoral agents.

The ultimate cause of narcolepsy is not known. How the depression of wakefulness is brought about is in the realm of speculation; it appears to be a state of depression of the reticular activating system, possibly from a neurohumoral deficiency.

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**Dexedrine; Smith, Kline & French Laboratories.*
†Desoxyn, Abbott Laboratories.
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§Ritalin, CIBA Pharmaceutical Products Inc.

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R-WAVE VOLTAGE CHANGES IN RELATION TO ARTERIAL PRESSURE IN HYPERTENSIVE PATIENTS

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HIGH voltage of R waves in left precordial leads of the electrocardiogram has been proposed as a sign of left ventricular hypertrophy.[1,2] A high incidence of abnormally large R waves in V_5 has been reported in hypertensive patients with high diastolic arterial pressure.[3] A rise in blood pressure following infusion of *l*-norepinephrine in normotensive subjects,[4] and ligation of the aorta in animals,[5] has resulted in an increase in the amplitude of the R waves. Considerable reduction in the voltage of R waves has been observed following satisfactory treatment of hypertension with methonium compounds[6] and other antihypertensive agents.[7] These observations suggest that elevated arterial pressure may be an important factor in influencing the amplitude of R waves, but this relationship has not been adequately investigated.

The present study determines the possible effects that the lowering of arterial pressure exerts on the amplitude of R waves in left precordial leads of hypertensive patients whose electrocardiograms show evidence that meets the criteria for left ventricular hypertrophy as defined by Sokolow and Lyon.[1]

Methods and Material

Twenty hypertensive patients whose electrocardiograms showed increased voltages of R and S waves in leads V_5 and V_1, respectively, were studied at the Cleveland Clinic Hospital. All the patients had a mild to moderately severe hypertension that was benign in 13 patients, malignant in 1 patient, and associated with renal arterial lesions in 6 patients. Evidence of mild cardiac enlargement with some prominence of the left ventricle was present in the roentgenograms of 9 patients, whereas in those of 11 patients the cardiac size and configuration were normal.

By using the criteria of Sokolow and Lyon,[1] namely, the sum of voltages of R waves in V_5 and S waves in V_1 as greater than 35 mm., left ventricular hypertrophy could have been diagnosed in all the cases. The amplitude of R waves in V_5 or V_6 ranged from 19 to 40 mm., the mean value being 26.5 mm. Intraventricular conduction defect was not evident in any patient.

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Arterial pressure was lowered in all 20 patients by intravenous infusion of sodium nitroprusside administered according to the recommendations of Page, Corcoran, Dustan, and Koppanyi.[8] Arterial pressure was measured with a sphygmomanometer before the infusion of sodium nitroprusside and every 30 seconds thereafter. The arterial pressure was kept at various desired levels until electrocardiographic records were obtained. Control electrocardiograms were recorded for each patient, that is, six standard limb leads and six precordial leads, V_1 through V_6. Thereafter, during the infusion of sodium nitroprusside, only the precordial leads V_1 and V_5 or V_6 were recorded in 15 patients, and complete electrocardiograms of five patients at various desired levels of arterial pressure.

Results

In 19 of the 20 patients, lowering of arterial pressure with sodium nitroprusside resulted in a decrease of the amplitude of R waves in lead V_5. The reduction ranged from 3 to 19 mm., or from 14 to 49 per cent of the control values. In the one patient, no changes occurred. The average control amplitude of R waves in V_5 for all the patients was 26.5 mm. Following intravenous administration of sodium nitroprusside, this average amplitude was reduced to 18.9 mm., or 71.3 per cent of the control values. Reduction of the amplitude of the R waves was approximately proportional to the decrease in arterial pressure until low normotensive levels were achieved; further lowering of arterial pressure to hypotensive levels did not result in further reduction in the voltages of the R waves.

Changes in the voltages of S waves in V_1 or V_2 were not consistent. In one half of the patients an increase occurred, ranging from 1 to 6 mm., the mean increase being 11 per cent of the control values. In the other half the voltages were reduced from 1 to 8 mm., the mean reduction being 13.9 per cent of the control values. The sums of R waves in V_5 and S waves in V_1 were reduced in

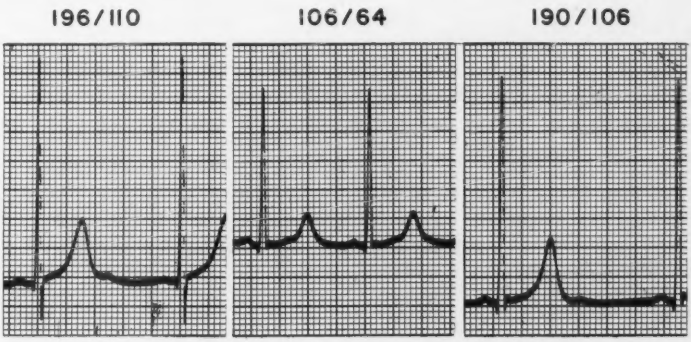

Fig. 1. Electrocardiograms (V_5) showing decreases in voltage of the R wave during normotensive period (after administration of sodium nitroprusside), and increases in voltage after hypertension returns, following termination of sodium nitroprusside administration.

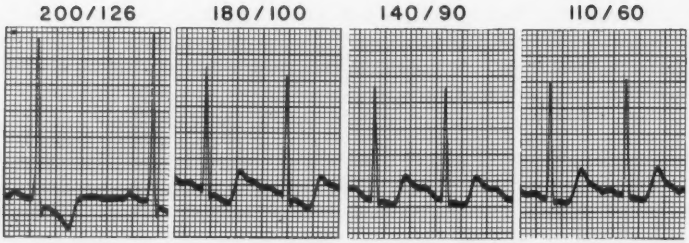

Fig. 2. Electrocardiograms (V_5) showing changes in R waves, S-T segments, and T waves during progressive lowering of blood pressure by administration of sodium nitroprusside.

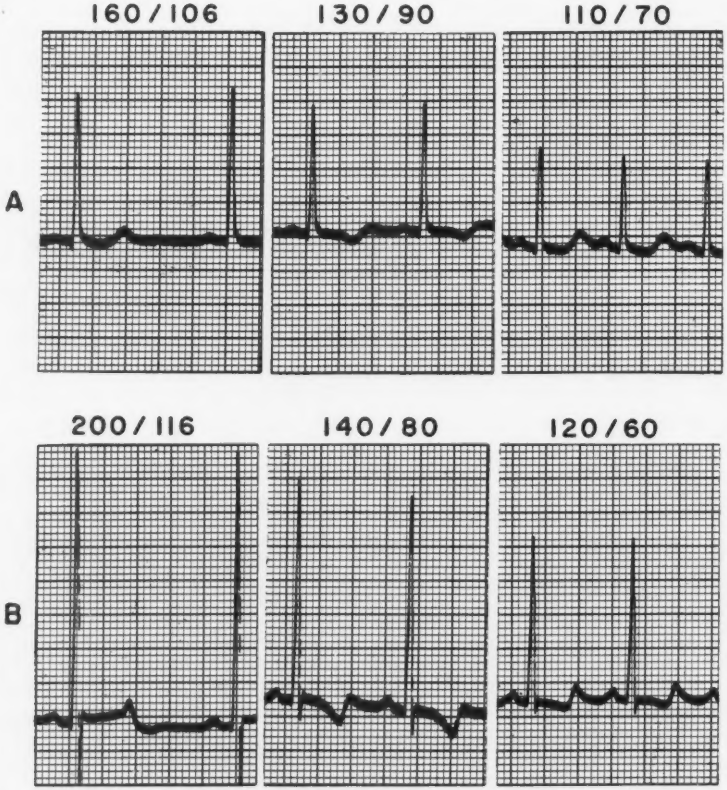

Fig. 3A and B. Electrocardiograms (V_5) showing R-wave and T-wave changes in two patients during lowering of blood pressure; inversion of previously upright T waves in records taken at blood pressure levels intermediate between control and normotensive periods.

all the patients when the arterial pressure was lowered to normotensive levels; the reduction ranged from 4 to 21 mm., the mean reduction being 15.6 per cent of the control values.

Complete electrocardiograms were recorded before and during infusion of sodium nitroprusside in five patients; the electric axis of the heart changed from horizontal to semivertical in three and to vertical in two patients.

The intrinsicoid deflection in left precordial leads was not affected. The changes of S-T segments and T waves in V_5 or V_6 *(Fig. 1)* were not significant in 15 patients. Of the other five patients, in one patient the S-T segments became less depressed, following progressive lowering of arterial pressure, and the T waves changed from inverted to predominantly upright *(Fig. 2);* in one patient the upright T wave became diphasic; in the other three patients, moderate reduction of arterial pressure resulted in inversion of the previously upright T waves, but further lowering of blood pressure was accompanied by diphasic or upright T waves *(Fig. 3).*

Discussion

Increased voltage of R waves in left precordial leads has been ascribed to an increased mass of left ventricular musculature[2,9] and has been proposed as a sign of left ventricular hypertrophy.[1,2] Although Doyle[6] observed a reduction in amplitude of R waves in hypertensive patients following treatment with hexamethonium compound, and suggested that this decrease was not necessarily due to involution of the hypertrophied muscle following control of hypertension, he concluded that this mechanism was the most probable explanation.

The results of the present study indicate that, in hypertensive patients, acute lowering of arterial pressure to low normal levels results in significant decreases in the voltages of R waves in V_5 and V_6, the decreases being approximately proportional to the degree of decrease in arterial pressure. When further decreases of arterial pressure from normotensive to hypotensive levels were achieved, further reduction of the voltages of R waves did not occur.

Since lowering of arterial pressure following long-term antihypertensive treatment has also resulted in reduction of the amplitude of R waves,[6,7] we believe that, because of its variability with the level of arterial pressure, the height of R waves in left precordial leads of hypertensive patients is not a valid sign of anatomic left ventricular hypertrophy. Similarly, although less variable, the summation of R waves in V_5 and of S waves in V_1 does not represent a reliable criterion for left ventricular hypertrophy in hypertensive patients. It seems that the voltages of S waves in V_1 or V_2 remain more or less stable and do not vary with the arterial pressure.

The mechanism by which lowering of arterial pressure results in reduction of voltage of R waves is not clear. The suggested factors influencing the height of R waves are the thickness of the left ventricle,[9] the direction of spread of depolar-

ization,[10] the distance of the exploring electrode from the surface of the heart,[11] and the stroke volume.[12] These factors, however, do not seem to explain the results of this study. The observed changes in the electric position of the heart also do not account for the reductions in R-wave voltages.

Summary

Reducing the arterial pressures with sodium nitroprusside in hypertensive patients was accompanied by significant decreases in R-wave voltages in left precordial leads. This effect should lead to caution in attributing high R-wave voltages to anatomic left ventricular hypertrophy in hypertensive patients.

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